Pituitary and peripheral hormone responses to T_3 administration during Antarctic residence

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Very little is known regarding hormonal adaptation in human subjects who are exposed to the extremes of temperature and light that are found in polar latitudes. We have previously reported a 50% elevation in the serum thyrotropin (TSH) response to thyrotropin-releasing hormone (TRH), a fall in serum total triiodothyronine (T_3) and free T_3 (fT_3), and no change in serum total thyroxine (T_4) or free T_4 (fT_4) after 42 wk of Antarctic cold exposure. To differentiate between central and peripheral mechanisms that may lead to these changes, we report the effect of sequentially increasing oral doses of T_3 (Cytomel) on serum T_3 and fT_3 levels and on the resultant attenuation of the TSH response to TRH in nine men before, during, and after 42 wk residence in Antarctica. Serum T_3 values basally and following the administration of 25, 50, and 75 μg/day of T_3 were lower after 42 wk of cold exposure (151 ± 4, 160 ± 8, 189 ± 10, and 222 ± 14 ng/dl, respectively, compared with control values of 160 ± 7, 178 ± 7, 202 ± 9, and 251 ± 19 ng/dl, respectively, $P < 0.05$). Likewise, the fT_3 values measured after these three increasing T_3 doses were also lower after 42 wk of cold exposure. The pituitary response to TRH was attenuated by each T_3 regimen (48 ± 6, 68 ± 4, and 77 ± 4% decreases in the control period), and this suppression was not different after 20 and 42 wk of Antarctic residence. Serum T_4 and fT_4 values were similar throughout the study. We conclude that the pituitary sensitivity to T_3 was unchanged during the study and that changes in TSH responsiveness and serum T_3 levels were likely due to changes in peripheral T_3 metabolism.

thyrotropin; thyrotropin-releasing hormone; 3,5,3′-triiodothyronine; cold adaptation

EUTHERMIC MAMMALS are uniquely characterized by their ability to maintain a constant core temperature despite variations in climatic conditions. Among other factors, mammalian nonshivering thermogenesis is thought to be regulated by iodothyronines (11, 38), glucocorticoids (8), catecholamines (1, 19, 25), opioid peptides (29), glucagon (34), hypothalamic neuronal efferents (14), and brown adipose tissue (3, 13). Adaptive responses of serum iodothyronines to a decline in environmental temperature have received a great deal of attention, not only because they can be easily studied in an in vivo model, but also because of their known importance in regulating thermogenesis.

Humans repeatedly exposed to a cold environment develop characteristic physiological changes, which some authors have called adaptive (21). However, earlier studies have not established consistent serum hormonal changes that correlate with these known physiological differences. One possible explanation for these conflicting results to date has been the application of widely disparate stimuli. Ambient temperature, altitude, duration, and interval between cold exposures, age, nutritional state, clothing, and physical activity all differ in these various reports.

We have previously reported a cohort of euthyroid human males exposed to an intermittent cold stimulus of known duration; an 11-mo sojourn (1980–1981) on the Antarctic continent. These subjects were studied before, during, and after 42 wk of continuous Antarctic residence. We described in this group, a 50% elevation in the plasma thyrotropin (TSH) response to thyrotropin-releasing hormone (TRH), a fall in serum total 3,5,3′-triiodothyronine (T_3) and free T_3 (fT_3), and no change in serum total thyroxine (T_4) or free T_4 (fT_4) during the Antarctic cold exposure (27). We feel that this constellation of thyroid hormone values represents an environmentally associated and as yet poorly understood change in thyroid hormone economy. We believe this model is distinctly different than the changes observed during starvation (4, 12), overfeeding (6), depression (7, 20), or the euthyroid sick syndrome (40). Konno et al. (18) have described a group of hypothyroid patients maintained on fixed doses of thyroxine who demonstrated an augmentation of the TSH response to TRH during the Japanese winter. However, we know of no euthyroid human studies that have prospectively measured the serum dose-response curve to oral T_3 or T_4 administration and the pituitary sensitivity to these hormones before and after prolonged cold exposure. We now report a different cohort, age and sex matched with our original subject population and who lived at the same Antarctic base under similar environmental conditions in a later calendar year (1982–1983), to further define the mechanisms that may account for our earlier observations. Possible explanations of these previous findings might include either an increased clearance of T_3, a decreased produc-

tion of T_3, or an altered sensitivity of the hypothalamic pituitary axis to endogenous T_3. We thus prospectively studied the responses to increasing doses of orally administered triiodothyronine (Cytomel, Smith Kline & French, Philadelphia, PA) of both serum T_3 and fT_3, and the suppression of the TSH response to TRH before, during, and at the completion of 42 wk of continuous Antarctic residence.

MATERIALS AND METHODS

Nine healthy Caucasian males (25 ± 1 yr), members of the 1982–1983 annual winter-over party at McMurdo Sound, Antarctica, were studied under varying climatic conditions, with each subject serving as his own control. Informed consent was obtained from all participants. All volunteers were within the height and weight standards for US Navy personnel during the entire period of the study. The mean ± SE body weights of the subjects before and after the study (81 ± 4 kg and 82 ± 4 kg, respectively) were not different.

The basal diet consisted of 2,000–2,500 kcalories (kcal), with ~40% as carbohydrate, 35% as protein, and 25% as fat. During the Antarctic residence, the calories consumed per subject increased to 3,000–3,500 kcal/day, but the relative contributions from carbohydrate, protein, and fat remained the same.

Basal and dynamic thyroid function testing were performed in September, 1982, during mission training in Port Hueneme, CA (i.e., at sea level and with average temperature of 20 ± 5°C). The subjects were then transported to McMurdo Sound, Antarctica, for duty. Thyroid testing was repeated at the completion of the austral summer (March of 1983), after 20 wk of exposure, and again at the end of the austral winter (August of 1983), after a total of 42 continuous wk of exposure.

Each subject wore standard military polar clothing during outdoor activity; however, the face and hands were often exposed with this uniform. The subjects were similar with regard to the amount of out-of-door exposure each experienced throughout the study (2.8 ± 0.7 h/day). Because of the physical nature of the base, each subject was exposed not <0.25 h/day on two separate occasions during each of 294 days of the study, thus serving as a model of multiple repeated environmental exposures. Ambient temperature was recorded during each evaluation period (Fig. 1). Each subject's cold exposure time per 24 h was also recorded and correlated to the observed hormonal changes. Indoor fluorescent lighting was used during the austral winter months, and all eight subjects maintained routine 8-h sleep/wake patterns, with an indoor temperature of 15.5–20.0°C.

At each study period (warm control, 20 and 42 wk), subjects underwent basal measurements of serum T_4, fT_4, T_3, T_3 resin uptake (T_3RU), TSH, and TSH response to TRH. At each study period, after obtaining basal samples, the subjects were administered sequentially increasing doses of T_3 at levels of 25, 50, and 75 μg/day respectively, on 3 successive days. The 25-μg/day dose of T_3 was divided into five doses of 5 μg; the 50-μg/day dose was divided into five doses of 12.5, 12.5, 10, 10, and 5 μg; and the 75-μg/day dose was divided into five doses of 25,

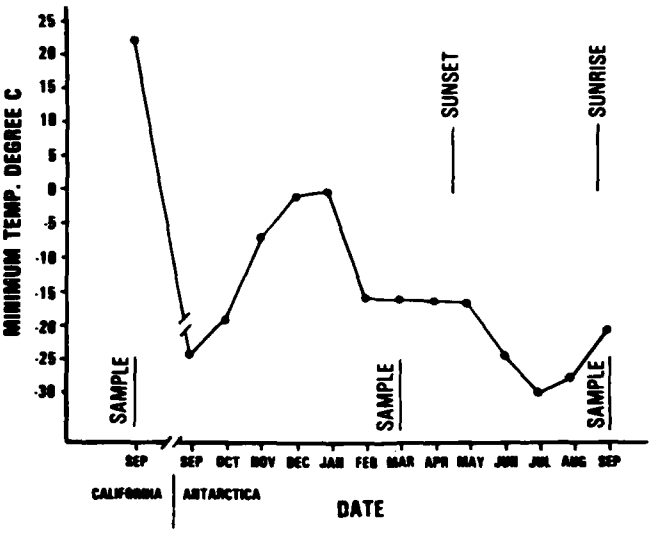

FIG. 1. Minimum ambient temperature (●) is shown for sampling periods in Port Hueneme, CA, and McMurdo, Antarctica.

12.5, 12.5, 12.5, and 12.5 μg. Doses were administered at 1000, 1400, 1800, 2200, and 0200 during the 3-day period. Pill boxes were collected and pills were counted to assure compliance with the protocol. This dosing interval was used to optimize the balance between near steady-state T_3 serum levels, a minimum of sleep deprivation (26), and maximal TSH suppression (41) as well as to allow comparison with similar dosing intervals previously published by our laboratory (4). Basally, before Cytomel, serum was collected for T_3, and a TSH stimulation test was carried out. At each dose level (25, 50, and 75 μg/day), serum was collected at 0800 for T_3, fT_3, and TSH, and a TRH stimulation test was performed. The TSH response to TRH was carried out in nonfasted subjects at 0800 on each of the 3 days by measuring the initial serum TSH value and the value at 15, 30, 45, and 60 min after the bolus intravenous administration of 250 μg of TRH (17, 31, 12). The integrated TSH response to TRH was expressed using Simpson's approximation for discrete intervals. All similar hormone samples were coassayed.

Serum T_4 (normal 5.3–10.5 μg/dl) and T_3 (normal 80–204 ng/dl) were measured commercially by radioimmunoassay (RIA) performed by Nichols Institute (Los Angeles, CA). Serum fT_4 (normal 1.3–3.8 ng/dl) and fT_3 (normal 260–480 pg/dl) levels, measured by dialysis technique, were also determined by Nichols Institute. Serum TSH was measured by RIA (normal 1.5–6 μIU/ml); Kallsted Laboratories, Austin, TX). The lower limit of the TSH assay was 1.5 μIU/ml. The T_3 resin uptake was measured by solid-phase ^{125}I radioassay (Diagnostic Products, Los Angeles, CA). The "normalized" free T_4 index was calculated as the T_3 resin uptake value divided by a normal pool T_3 resin uptake (0.35) and then multiplied by the total T_4.

Statistical analysis was performed by using analysis of variance with repeated measures and Duncan's multiple-range test for differences between means (Statpak version 4.1, Northwest Analytical, Portland, OR). Generation of three single variable regression curves (one con-

trol, one at 20 wk, and one at 42 wk) of the serum T_3 response to incremental doses of T_3 produced the family of T_3 dose-response curves shown in Fig. 3. Comparisons between the curves were done by two-way analysis of variance with two repeated measures.

RESULTS

Serum T_4 and fT_4 (Table 1)

The mean ± SE T_4 value of 6.0 ± 0.4 μg/dl obtained after 20 wk of exposure and the T_4 value of 6.3 ± 0.3 μg/dl after 42 wk of exposure were not different than the control T_4 of 6.4 ± 0.4 μg/dl measured in a warm climate. The fT_4 remained unchanged after 20 and 42 wk of exposure (1.7 ± 0.1 and 1.9 ± 0.1 ng/dl, respectively), when these were compared with a control value of 2.0 ± 0.1 ng/dl.

T_3 RU and fT_4 Index (Table 1)

The T_3RU increased slightly throughout the observation period, from a control value of 31.2 ± 1.0% to a value of 33.9 ± 0.8% after 42 wk of cold exposure ($P < 0.05$). There were no differences between the values obtained after 20 and 42 wk of polar living. The free T_4 index (fT_4I) remained unchanged through the study period.

Serum T_3 (Table 2, Figs. 2 and 3)

The serum T_3 values, measured basally and after each incremental dose of oral T_3, were lower after 20 ($P = 0.01$) and 42 ($P = 0.05$) wk compared with control values by two-way analysis of variance with two repeated measures ($P = 0.03$), when all doses and dates are combined.

Serum fT_3 (Table 2, Fig. 4)

The serum fT_3 after T_3 administration tended to decline after 20 wk; however, this change was not statistically significant. The fT_3 declining trend, which continued during the measurements at 42 wk, was significantly different with respect to date when analyzed by two-way analysis of variance with two repeated measures ($P = 0.009$).

T_3/T_4 Ratio (Table 1)

The T_3/T_4 ratio measured at each seasonal interval (control, 20 and 42 wk of exposure) before the administration of oral T_3 was unchanged 25.6 ± 1.6 × 10^{-3}, 25.6 ± 2.0 × 10^{-3}, and 24.1 ± 1.1 × 10^{-3}, respectively.

TSH Response to TRH (Fig. 5)

Basal: without oral T_3 administration. Static TSH serum levels, after 20 and 42 wk of cold exposure, were 2.9 ± 0.4 and 2.2 ± 0.3 μIU/ml, respectively, and these values were not statistically different than the warm control basal value of 2.1 ± 0.3 μIU/ml. However, the integrated TSH response to TRH markedly increased from a control value of 502 ± 77 to 699 ± 70 $\mu IU \cdot min^{-1} \cdot ml^{-1}$ after 20 wk, and this value remained elevated with a value of 688 ± 67 $\mu IU \cdot min^{-1} \cdot ml^{-1}$ after 42 wk of Antarctic residence ($P < 0.01$). The mean (±SE) paired increases of the TSH response over control non-T_3-treated values were 54 ± 14 and 52 ± 14% after 20 and 42 wk, respectively.

After oral T_3 administration (Fig. 5). The TSH response was equally attenuated by oral T_3 both before and after cold exposure. The absolute integrated TSH response values during suppression with 25, 50, and 75 μg/day of T_3 remained higher when measured after 20 wk of exposure (386 ± 33, 183 ± 15, 121 ± 10 $\mu IU \cdot min^{-1} \cdot ml^{-1}$) compared with warm climate control values of 134 ± 24, 140 ± 14, 96 ± 4 $\mu IU \cdot min^{-1} \cdot ml^{-1}$ (Fig. 5). The absolute TSH response values after 42 wk (373 ± 50, 191 ± 20, 117 ± 8 $\mu IU \cdot min^{-1} \cdot ml^{-1}$, respectively) remained elevated above warm climate controls ($P < 0.05$) but were not different than corresponding values obtained after 20 wk of exposure. However, the mean percentage suppression of the TSH response in our subjects at each dose level of T_3 was not different either before or after cold exposure. Before deployment, the TSH response was suppressed by 48 ± 6, 68 ± 4, and 77 ± 4% after respective doses of 25, 50, and 75 μg/day. These decrements did not change

TABLE 1. *Serum total T_4, fT_4, T_3RU, fT_4I, and T_3/T_4 without T_3 during control and after 20 and 42 wk of Antarctic residence*

Subject No.	Control					20 Wk					42 Wk				
	T_4, μg/dl	fT_4, ng/dl	T_3/T_4, ×10^{-3}	T_3RU, %	fT_4I, %	T_4, μg/dl	fT_4, ng/dl	T_3/T_4, ×10^{-3}	T_3RU, %	fT_4I, %	T_4, μg/dl	fT_4, ng/dl	T_3/T_4, ×10^{-3}	T_3RU, %	fT_4I, %
1	7.7	2.1	21.5	37.2	8.2	6.5	1.5	25.8	37.9	7.0	7.2	2.0	21.5	36.4	7.5
2	6.6	1.7	21.5	29.7	5.6	6.3	2.1	22.7	31.2	5.6	7.1	1.6	21.1	30.8	6.3
3	5.5	1.9	25.1	33.9	5.3	5.5	1.9	23.8	36.1	5.7	5.9	2.1	21.9	37.1	6.3
4	6.1	2.0	30.0	28.9	5.0	6.9	2.0	22.5	32.9	6.5	6.1	1.8	27.7	33.2	5.8
5	7.9	2.3	21.6	29.1	6.6	7.8	2.2	16.9	34.3	7.6	7.9	2.2	20.8	33.0	7.5
6	IS	IS	IS	33.2	IS	IS	IS	IS	IS	IS	6.3	2.1	22.2	IS	IS
7	6.9	2.7	23.4	30.9	6.1	5.7	1.5	27.4	33.4	5.4	5.6	1.6	24.1	33.7	5.4
8	4.8	1.6	27.7	29.1	4.0	5.0	1.6	30.2	35.9	5.1	5.3	IS	29.8	32.8	5.0
9	5.7	1.7	34.0	29.?	4.8	4.3	1.1	35.3	37.6	4.6	5.6	1.6	27.9	IS	IS
Means	6.4	2.0	25.6	31.2	5.7	6.0	1.7	25.6	34.9*	5.9	6.3	1.9	24.1	33.9*	6.3
± SE	±0.4	±0.1	±1.6	±1.0	±0.5	±0.4	±0.1	±2.0	±0.8	±0.4	±0.3	±0.1	±1.1	±0.8	±0.4

T_4, total thyroxine; fT_4, free thyroxine; T_3, total triiodothyronine; T_3RU, T_3 resin uptake; fT_4I, normalized free T_4 index; T_3/T_4, total T_3-to-total T_4 ratio; IS, insufficient sample. * $P < 0.05$ compared with control.

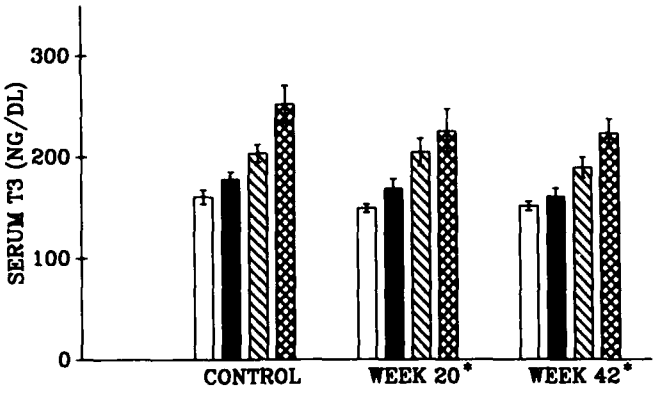

FIG. 2. Serum (mean ± SE) levels of total T_3 without T_3 □ and after 25 (▦), 50 (▩), and 75 μg/day (▩) of oral T_3 measured as control in a warm climate and after 20 and 42 wk of cold exposure. * $P \leq 0.05$ compared with control by using 2-way analysis of variance with respect to *treatments 1* (date) and *2* (dose).

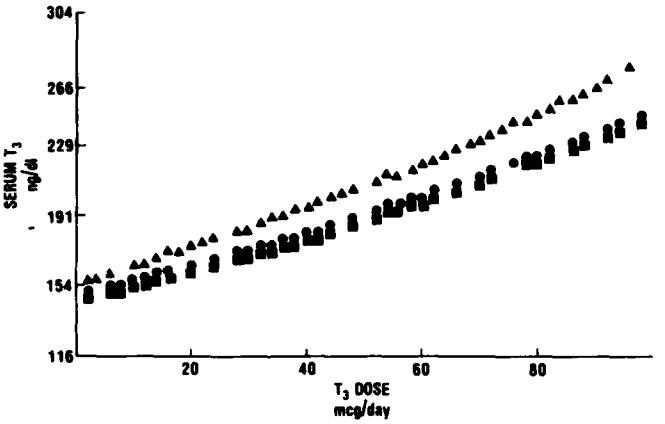

FIG. 3. This figure shows a computer-derived serum dose-response curve of serum T_3 to oral T_3, calculated in a control climate (▲) and after 20 (●) and 42 wk of cold exposure (■). Dose response of T_3 after 20 and 42 wk is different from basal ($P < 0.05$).

with the same dose of T_3 after 20 and 42 wk. The values were 44 ± 2, 73 ± 2, and 82 ± 2%, respectively after 20 wk, and 47 ± 3, 72 ± 1, and 82 ± 2%, respectively after 42 wk of Antarctic residence. The calculated dose needed to suppress the TSH response by 50% is 29 ± 4 μg/day and this dose was not different before or after 42 wk of cold exposure.

Exposure and Diet

Even though the amount of consumed calories increased, there was no significant increase in body weight throughout the observation period. Occupationally related activities were similar in both the control and cold environment. All members of the party were similarly exposed to the cold environment (2.8 ± 0.7 h/day). There was no correlation between an individual's mean exposure time per day and any hormonal changes noted throughout the 42 wk of polar living.

DISCUSSION

The population residing in the polar latitudes has increased recently since the discovery of fossil fuel deposits in these regions. The environments near the geographic poles are marked by prolonged periods of darkness or sunlight and extended winters with severely cold temperatures. Adaptive responses of serum thyroid hormones in a cold environment have received considerable attention in the past, and in this paper we extend these observations by measurement of the serum T_3 response to oral T_3 and the pituitary response to this hormone before and after Antarctic residence.

Serum total and free T_4 levels remained unchanged in our study group, consistent with our earlier findings (27). Unchanged serum levels of T_4 during seasonal variation and during continuous cold exposure have been reported in most (17, 23) but not all (35) previous studies. However, in hypothyroid patients on T_4 replacement, Konno (18) showed that serum T_4 tended to be lower during the Japanese winter when compared with paired summer controls.

The serum total and free T_3 values (after T_3 administration) in the present study were lower when measured after 42 wk of cold exposure compared with basal warm climate controls, confirming our earlier description (27). Vining et al. (39) have published data consonant with our findings in an Australian Antarctic cohort. Their subjects had lower serum T_3 values in winter compared with summer; however, they did not measure either fT_3 or basal values before departing for Antarctica. Dessypris et al. (9) observed a lower serum total T_3 in the inhabitants of the Arctic regions of Finland, compared with their matched southern counterparts. In contrast to these findings Nagata et al. (23) have reported increased levels of serum total T_3 in the natives of Kijimadaira, Japan, in winter compared with values obtained during a warm summer. This group of natives, however, was poorly clothed and lived in inadequate housing that resulted in nearly continuous cold exposure during the group's 3-mo winter. Our subjects varied from this group in that they were well clothed and exposed intermittently to a cold environment for 11 continuous months.

The augmented TSH response to TRH observed in the present study confirms our earlier observations (27). This test of TSH reserve is reliably reproducible (6–12% cv) in the same subjects (17, 31). An elevated nonstimulated serum TSH in Antarctic residents and in the residents of northern Finland has been observed (9, 39). However, the insensitivity of our TSH assay in the low ranges may have precluded us from detecting basal nonstimulated differences. Others have not been able to detect a change in the seasonal TSH response to TRH in normal subjects residing in midlatitude temperate climates (17, 31). The differences between these studies and our own are most likely a result of the severity of cold environment in the polar latitudes compared with midlatitude temperate climates.

The possible mechanisms to account for decreased serum T_3 and fT_3 levels include decreased production of T_3 (4, 40), increased metabolic clearance of T_3 (2, 5, 33), and decreased absorption of oral T_3 after chronic cold exposure and/or circadian variation (24). Any postulated mechanism must take into account a balanced T_4 economy, because T_4 was unchanged.

TABLE 2. *Serum total and free T_3 with T_3 administration during control and after 20 and 42 wk of Antarctic residence*

Subject No.	Control				20 Wk*				42 Wk*			
	Dose No.				Dose No.†				Dose No.†			
	0	25	50	75	0	25	50	75	0	25	50	75
					Total T_3, ng/dl							
1	166	218	187	228	168	201	186	237	155	161	209	206
2	142	192	229	309	143	197	240	293	150	188	244	260
3	138	156	183	217	131	150	176	179	129	139	166	184
4	183	187	233	294	155	190	272	263	169	196	193	227
5	171	173	241	341	132	175	253	318	164	184	211	312
6	151	181	195	276	148	182	204	262	140	158	198	234
7	161	167	210	219	156	162	171	197	135	148	160	200
8	133	149	174	196	151	141	166	128	158	142	154	202
9	194	176	170	180	152	116	165	144	156	125	162	174
Means ± SE	160±7	178±7	202±9	251±19	148±4	168±9	204±14	225±22	151±4	160±8	189±10	222±14
					Free T_3, pg/dl							
1		486	472	541		494	478	606		468	531	572
2		455	494	581		376	502	701		422	561	IS
3		395	511	610		403	463	498		350	391	482
4		449	533	659		460	647	636		418	418	525
5		IS	530	643		IS	547	764		IS	505	723
6		444	382	579		397	398	515		288	375	432
7		340	463	440		IS	407	472		IS	407	441
8		382	402	492		374	415	IS		IS	367	483
9		433	340	IS		325	438	318		269	360	445
Means ± SE		423±17	459±23	568±26		404±21	477±27	564±50		369±33	435±26	513±34

Oral triiodothyronine (T_3) doses were measured in μg/day. IS, insufficient sample. * $P < 0.05$ compared with control; † $P < 0.05$ for each dose compared with control (analysis by 2-way ANOVA with 2 repeated measures).

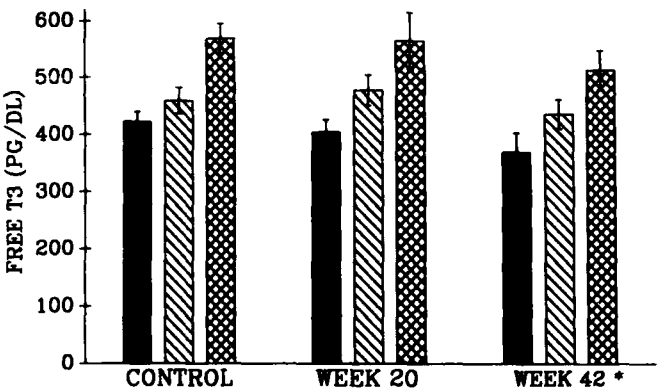

FIG. 4. Serum (mean ± SE) free T_3 was measured as in Fig. 2, after 25 (■), 50 (▨), and 75 μg (▩) of oral T_3, * $P < 0.05$ compared with control by using 2-way analysis of variance with respect to date as a treatment.

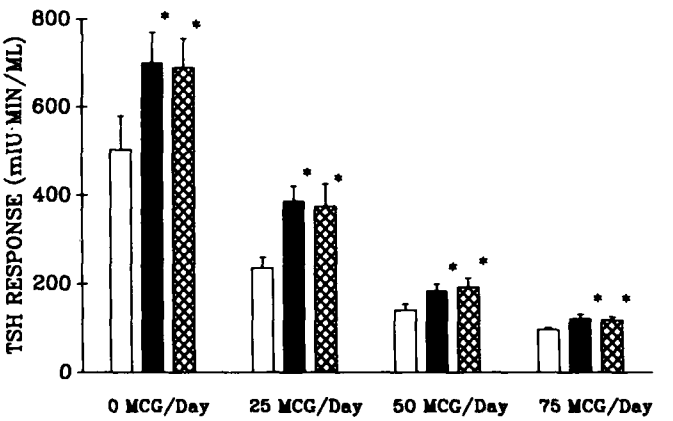

FIG. 5. Integrated thyrotropin (TSH) response to thyrotropin-releasing hormone (mean ± SE) measured in 9 subjects before and after 25, 50, and 75 μg/day of T_3. This response was measured in a warm control climate (□) and after 20 (■) and 42 wk (▩) cold exposure. There was no difference between results obtained after 20 and 42 wk cold exposure. MCG, microgram. * $P < 0.05$ compared with warm control climate values.

We feel that decreased production of T_3 as found in the sick euthyroid syndrome or during hypocaloric feeding cannot account for our findings because serum T_3 in our subjects was not "normalized" after oral T_3 administration (4, 16, 40). Additionally, if decreased peripheral production of T_3 was a significant contributing factor in this setting, one should observe a lowering of the T_3/T_4 ratio and an increase in reverse T_3, neither of which has been noticed in the previous group observed in this setting (27). Also, the increased caloric consumption seen in our subjects should lead to increased serum T_3 levels as demonstrated by Danforth et al. (6). However, the present study documented lower serum T_3 levels, leading us to implicate other factors to explain the changes described.

Increased degradation of T_3 and T_4 has been described in rodent models chronically exposed to cold (2, 33). Iodothyronine disposal may be increased by a number of mechanisms including nonspecific hepatic induction as occurs with phenytoin (Dilantin) (36) or catecholamines (22) or via increased enterohepatic circulation (5). It is interesting to note that elevated plasma catecholamine levels do occur during acute cold exposure (25). If increased disposal of T_3 plays a significant role in our observations, we would expect to find lowered serum T_3

after administered oral T_3, a finding we describe herein. Ingbar et al. (15) suggest such a mechanism during severe and prolonged human cold exposure by using iodine clearance studies, when they described increased thyroidal iodide turnover in cold-exposed human subjects. Also, in support of a proposed clearance mechanism, Konno et al. (18) showed an augmented TSH response to TRH and somewhat lowered serum T_4 in replaced hypothyroid subjects during the Japanese winter when compared with summer controls. Either increased peripheral disposal of T_4 or decreased T_4 absorption might have accounted for these observations. Similarly, Rastogi et al. (30) reported increased urinary fT_3 and fT_4 levels in paired subjects studied in winter compared with summer without changes in serum total T_3 or total T_4, suggesting either a seasonal change in the binding of these thyroid hormones and/or a small decrease in the half-life of thyroid hormones in winter.

Although we cannot exclude decreased absorption of orally administered T_3 as a possible mechanism, this explanation is unlikely in that T_3 is consistently well absorbed by the normal gastrointestinal mucosa (10, 32, 41). Circadian nocturnal elevations in the T_3/T_4 ratio have been described by Nimalasuriya et al. (24). However, we do not feel that the changes in light exposure affected our findings, in that we describe a decrease in T_3 and no change in the T_3/T_4 ratio during both the dark (42-wk) and light (20-wk) period without a significant difference between these measurements.

Mechanisms by which the augmented TSH response occurs may include a circadian or diurnal variation in human TSH or T_3 (24, 30). Our data, however, were all obtained at the same clock time and show no difference between exposure to 24 h of daylight (after 20 wk of exposure) or 24 h of darkness (after 42 wk of exposure) on this response. The physical and social isolation found during Antarctic duty is a possible but somewhat unlikely contributing factor based on the known alterations in thyroid economy that occurs during depression. In this emotional setting the TSH response to TRH is decreased, not increased as we have found (7, 20). However, we can find no specific studies that have investigated thyroid function during confinement alone. Additionally, an increase in iodine in the diet may increase the TSH response to TRH, as Vagenakis et al. (37) describe, with an associated decrease in serum T_4 and T_3 as well as an elevation in unstimulated TSH. However, in our present study, no change in serum T_4 or basal levels of TSH were observed, and iodine intake did not change to our knowledge.

Sawin et al. (32) have described a 50% decrease in the TSH response to TRH measured 2 h after a mean dose of 29 μg/day of oral T_3. Our findings that 29 $\pm$ 4 μg/day suppress 50% of the TSH response both in a warm control climate and a polar setting are similar and in agreement with Sawin et al. (32). Thus there appears to be no change in the hypothalamic pituitary sensitivity to oral T_3 after cold exposure when compared with either basal warm climate controls or previously published controls (32). The absence of a change in the sensitivity of the hypothalamic pituitary axis coupled with lower serum T_3 and fT_3 levels before and after oral T_3 administration implies an increased metabolic clearance of T_3 and a decreased negative feedback on TSH secretion by circulating T_3. The specific metabolic implications of these findings and how they may relate to human environmental adaptation require further study.

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